# CENTER FOR DRUG EVALUATION AND RESEARCH

**Approval Package for:**

**Application Number : 074543**

**Trade Name : ALBUTEROL SULFATE INHALATION SOLUTION 0.5% (BASE)**

**Generic Name: Albuterol Sulfate Inhalation Solution 0.5%(base)**

**Sponsor : Hi-Tech Pharmacal Co., Inc.**

**Approval Date: January 15, 1998**

CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION 074543**

# CONTENTS

| | Included | Pending Completion | Not Prepared | Not Required |
|---|---|---|---|---|
| **Approval Letter** | X | | | |
| **Tenative Approval Letter** | | | | |
| **Approvable Letter** | | | | |
| **Final Printed Labeling** | X | | | |
| **Medical Review(s)** | | | | |
| **Chemistry Review(s)** | X | | | |
| **EA/FONSI** | | | | |
| **Pharmacology Review(s)** | | | | |
| **Statistical Review(s)** | | | | |
| **Microbiology Review(s)** | | | | |
| **Clinical Pharmacology Biopharmaceutics Review(s)** | | | | |
| **Bioequivalence Review(s)** | X | | | |
| **Administrative Document(s)** | | | | |
| **Correspondence** | | | | |

# CENTER FOR DRUG EVALUATION AND RESEARCH

**Application Number 074543**

## APPROVAL LETTER

ANDA 74-543

JAN 15 1998

Hi-Tech Pharmacal Co., Inc.
Attention: Elan Bar-Giora
369 Bayview Avenue
Amityville, NY 11701

Dear Sir:

This is in reference to your abbreviated new drug application dated September 19, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Albuterol Sulfate Inhalation Solution, 0.5% (base).

Reference is also made to your amendments dated November 5, and December 4 and 18, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined that your Albuterol Sulfate Inhalation Solution 0.5% is bioequivalent and, therefore, therapeutically equivalent to that of the listed drug (Proventil® Inhalation Solution 0.5% of Schering Corp.).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

1-15-98

cc: ANDA 74-543
Division File
Field Copy
HFD-600/Reading File
HFD-92
HFD-210/B.Poole
HFD-610/J.Phillips
HFD-330

Endorsements:

HFD-625/M.Shaikh/12/23/97 (See attached)
HFD-625/M.Smela/12/23/97
HFD-617/S.O'Keefe/PM/
HFD-613/J.Grace/
HFD-613/C.Holquist/12/23/97
HFD-640/AHigh/
x:\new\firmsnz\hitech\ltrs&rev\74543app.ltr
F/T by: bc/1-13-98

APPROVED

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 074543

## FINAL PRINTED LABELING

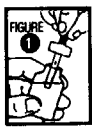
Albuterol Sulfate Inhalation Solution

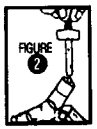
H-T

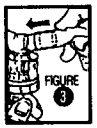
H-T

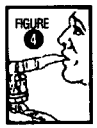
**Patient's Instructions For Use**
**Note: The Albuterol Sulfate Inhalation Solution contained in the 20mL multiple-dose bottle is concentrated and must be diluted.**
**Read complete instructions carefully before using.**

1. Draw 0.5 mL of Albuterol Sulfate Solution for Inhalation into the specially marked dropper that comes with each multi-dose bottle (Figure 1).
2. Squeeze the solution into the nebulizer reservoir through the appropriate opening (Figure 2).
3. Add 2.5 mL of sterile normal saline solution, as your physician has directed.
4. Gently swirl the nebulizer to mix the contents and connect it with the mouthpiece or face mask (Figure 3).
5. Connect the nebulizer to the compressor.
6. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 4) (or put on the face mask); and turn the compressor on.
7. **Breathe as calmly, deeply, and evenly** as possible until no more mist is formed in the nebulizer chamber (about 5-15 minutes). At this point, the treatment is finished.
8. Clean the nebulizer (see manufacturer's instructions).
   Note: Use only as directed by your physician. More frequent administration or higher doses are not recommended.
   (Lot number and expiration date are imprinted on the top flap.)




# Albuterol Sulfate Inhalation Solution 0.5%* 5 mg/mL*

**STERILE**

# Albuterol Sulfate Inhalation Solution 0.5%* 5 mg/mL*

NDC 50383-741-20

**STERILE**

***Potency expressed as albuterol**

**DILUTE BEFORE USE**
**FOR ORAL INHALATION ONLY**

**Attention Pharmacist:**
Detach "Patient's Instructions for Use" from package insert and dispense with solution.

**CAUTION: Federal law prohibits dispensing without prescription.**

**20 mL with calibrated dropper**

**USUAL DOSAGE:** See package insert.

**Each mL contains:**

albuterol sulfate, equivalent to 5 mg albuterol in an aqueous solution containing benzalkonium chloride; sulfuric acid used to adjust pH between 3 and 5.

Read accompanying instructions carefully.

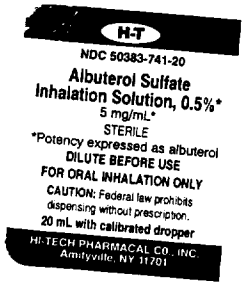
**Store between 2° and 25°C (36° and 77°F).**

HI-TECH PHARMACAL CO. INC.
Amityville, NY 11701

0 40017-741-20 6

3.3

C1 1998




**Albuterol Sulfate**
**Inhalation Solution, 0.5%***
**STERILE**

**Each mL contains:** albuterol sulfate, equivalent to 5 mg albuterol in an aqueous solution containing benzalkonium chloride; sulfuric acid used to adjust pH between 3 and 5.

**USUAL DOSAGE:** See package insert. Read accompanying directions carefully.

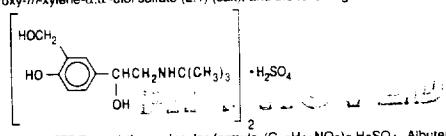
Store between 2° and 25° C (36° and 77° F).

# STERILE
## (*Potency expressed as albuterol)

JAN 15 1998

**DESCRIPTION**

Albuterol Sulfate Inhalation Solution contains albuterol sulfate, USP, the racemic form of albuterol and a relatively selective beta$_2$-adrenergic bronchodilator (see **CLINICAL PHARMACOLOGY** section below). Albuterol sulfate has the chemical name $\alpha^1$-[(*tert*-Butylamino) methyl]-4-hydroxy-*m*-xylene-$\alpha,\alpha'$-diol sulfate (2:1) (salt), and the following structural formula:



Albuterol sulfate has a molecular weight of 576.71 and the molecular formula $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$. Albuterol sulfate is a white crystalline powder, soluble in water and slightly soluble in alcohol.

The World Health Organization's recommended name for albuterol base is salbutamol.

Albuterol Sulfate Inhalation Solution, 0.5% is in concentrated form. Dilute 0.5 mL of the solution to 3 mL with sterile normal saline solution prior to administration.

Each mL of Albuterol Sulfate Inhalation Solution, 0.5% contains albuterol in a sterile, aqueous solution containing benzalkonium chloride; sulfuric acid is used to adjust the pH to between 3 and 5. Albuterol Sulfate Inhalation Solution, 0.5% contains no sulfiting agents. It is supplied in 20 mL bottles.

Albuterol Sulfate Inhalation Solution is a clear, colorless to light yellow sterile solution.

**CLINICAL PHARMACOLOGY**

The prime action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5'-adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). The cyclic AMP thus formed mediates the cellular responses. *In vitro* studies and *in vivo* pharmacologic studies have demonstrated that albuterol has a preferential effect on beta$_2$-adrenergic receptors compared with isoproterenol. While it is recognized that beta$_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, recent data indicate that 10% to 50% of the beta receptors in the human heart may be beta$_2$ receptors. The precise function of these receptors, however, is not yet established. Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes.

Albuterol is longer acting than isoproterenol in most patients by any route of administration because it is not a substrate for the cellular uptake processes for catecholamines nor for catechol-*O*-methyl transferase.

Studies in asthmatic patients have shown that less than 20% of a single albuterol dose was absorbed following either IPPB or nebulizer administration; the remaining amount was recovered from the nebulizer and apparatus and expired air. Most of the absorbed dose was recovered in the urine 24 hours after drug administration. There was a significant dose-related response in $FEV_1$ and peak flow rate (PFR). It has been demonstrated that following oral administration of 4 mg albuterol, the elimination half-life was 5 to 6 hours.

Animal studies show that albuterol does not pass the blood-brain barrier. Recent studies in laboratory animals (minipigs, rodents, and dogs) recorded the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines were administered concurrently. The significance of these findings when applied to humans is currently unknown.

In controlled clinical trials, most patients exhibited an onset of improvement in pulmonary function within 5 minutes as determined by $FEV_1$. $FEV_1$ measurements also showed that the maximum average improvement in pulmonary function usually occurred at approximately 1 hour following inhalation of 2.5 mg of albuterol by compressor-nebulizer, and remained close to peak for 2 hours. Clinically significant improvement in pulmonary function (defined as maintenance of a 15% or more increase in $FEV_1$ over baseline values) continued for 3 to 4 hours in most patients and in some patients continued up to 6 hours.

In repetitive dose studies, continued effectiveness was demonstrated throughout the 3-month period of treatment in some patients.

**INDICATIONS AND USAGE**

Albuterol Sulfate Inhalation Solution is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease and acute attacks of bronchospasm.

**CONTRAINDICATIONS**

Albuterol Sulfate Inhalation Solution is contraindicated in patients with a history of hypersensitivity to any of its components.

**WARNINGS**

As with any other inhaled beta-adrenergic agonists, Albuterol Sulfate Inhalation Solution can produce paradoxical bronchospasm, which can be life threatening. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs and with the home use of sympathomimetic nebulizers. It is, therefore, essential that the physician instruct the patient in the need for further evaluation if his/her asthma becomes worse. In individual patients, any beta$_2$-adrenergic agonist, including albuterol inhalation solution and solution for inhalation, may have a clinically significant cardiac effect.

Immediate hypersensitivity reactions may occur after administration of albuterol as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

**PRECAUTIONS**

**General:** Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension, in patients with convulsive disorders, hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Additionally, beta-agonists, including albuterol, when given intravenously may cause a decrease in serum potassium, possibly through intracellular shunting. The decrease is usually transient, not requiring supplementation. The relevance of these observations to the use of Albuterol Sulfate Inhalation Solution is unknown.

To avoid contaminating the multi-dose bottle of Albuterol Sulfate Inhalation Solution, proper aseptic technique should be used when withdrawing and delivering the dose into the nebulizer.

**Information For Patients:** The action of Albuterol Sulfate Inhalation Solution may last up to 6 hours and therefore it should not be used more frequently than recommended. Do not increase the dose or frequency of medication without medical consultation. If symptoms get worse, medical consultation should be sought promptly. While taking Albuterol Sulfate Inhalation Solution, other anti-asthma medicines should not be used unless prescribed.

See illustrated **"Patient's Instructions for Use."**

**PHARMACIST - DETACH HERE AND GIVE LOWER PORTION TO PATIENT**

---

### Patient's Instructions for Use

**ALBUTEROL SULFATE INHALATION SOLUTION, 0.5%***

*Potency expressed as albuterol

**Note: The Albuterol Sulfate Inhalation Solution contained in the 20 mL multiple-dose bottle is concentrated and must be diluted.**

**Read complete instructions carefully before using.**

Figure 1

1. Draw 0.5 mL of Albuterol Sulfate Inhalation Solution into the specially marked dropper that comes with each multi-dose bottle (Figure 1).
2. Squeeze the solution into the nebulizer reservoir through the appropriate opening (Figure 2).
3. Add 2.5 mL of sterile normal saline solution, as your physician has directed.
4. Gently swirl the nebulizer to mix the contents and connect it with the mouthpiece or face mask (Figure 3).
5. Connect the nebulizer to the compressor.
6. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 4) (or put on the face mask); and turn the compressor on.
7. Breathe as calmly, deeply, and evenly as possible

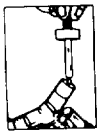


Figure 2

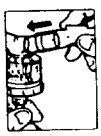


Figure 3

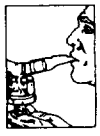


Figure 4

6 hours.

In repetitive dose studies, continued effectiveness was demonstrated throughout the 3-month period of treatment in some patients.

**INDICATIONS AND USAGE**

Albuterol Sulfate Inhalation Solution is indicated for the relief of bronchospasm in patients with reversible obstructive airway disease and acute attacks of bronchospasm.

**CONTRAINDICATIONS**

Albuterol Sulfate Inhalation Solution is contraindicated in patients with a history of hypersensitivity to any of its components.

**WARNINGS**

As with any other inhaled beta-adrenergic agonists, Albuterol Sulfate Inhalation Solution can produce paradoxical bronchospasm, which can be life threatening. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs and with the home use of sympathomimetic nebulizers. It is, therefore, essential that the physician instruct the patient in the need for further evaluation if his/her asthma becomes worse. In individual patients, any beta$_2$-adrenergic agonist, including albuterol inhalation solution and solution for inhalation, may have a clinically significant cardiac effect.

Immediate hypersensitivity reactions may occur after administration of albuterol as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema.

**PRECAUTIONS**

**General:** Albuterol, as with all sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension, in patients with convulsive disorders, hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.

Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis. Additionally, beta-agonists, including albuterol, when given intravenously may cause a decrease in serum potassium, possibly through intracellular shunting. The decrease is usually transient, not requiring supplementation. The relevance of these observations to the use of Albuterol Sulfate Inhalation Solution is unknown.

To avoid contaminating the multi-dose bottle of Albuterol Sulfate Inhalation Solution, proper aseptic technique should be used when withdrawing and delivering the dose into the nebulizer.

**Information For Patients:** The action of Albuterol Sulfate Inhalation Solution may last up to 6 hours and therefore it should not be used more frequently than recommended. Do not increase the dose or frequency of medication without medical consultation. If symptoms get worse, medical consultation should be sought promptly. While taking Albuterol Sulfate Inhalation Solution, other anti-asthma medicines should not be used unless prescribed.

See illustrated **"Patient's Instructions for Use."**

**PHARMACIST - DETACH HERE AND GIVE LOWER PORTION TO PATIENT**

## Patient's Instructions for Use

**ALBUTEROL SULFATE INHALATION SOLUTION, 0.5%***

*Potency expressed as albuterol

**Note: The Albuterol Sulfate Inhalation Solution contained in the 20 mL multiple-dose bottle is concentrated and must be diluted.**

**Read complete instructions carefully before using.**

Figure 1

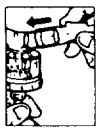


Figure 3

1. Draw 0.5 mL of Albuterol Sulfate Inhalation Solution into the specially marked dropper that comes with each multi-dose bottle (Figure 1).
2. Squeeze the solution into the nebulizer reservoir through the appropriate opening (Figure 2).
3. Add 2.5 mL of sterile normal saline solution, as your physician has directed.
4. Gently swirl the nebulizer to mix the contents and connect it with the mouthpiece or face mask (Figure 3).
5. Connect the nebulizer to the compressor.
6. Sit in a comfortable, upright position; place the mouthpiece in your mouth (Figure 4) (or put on the face mask); and turn the compressor on.
7. **Breathe as calmly, deeply, and evenly** as possible until no more mist is formed in the nebulizer chamber (about 5-15 minutes). At this point, the treatment is finished.
8. Clean the nebulizer (see manufacturer's instructions).

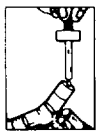


Figure 2

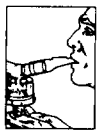


Figure 4

**Drug Interactions:** Other sympathomimetic aerosol bronchodilators or epinephrine should not be used concomitantly with albuterol.

Albuterol should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of albuterol on the vascular system may be potentiated.

Beta-receptor blocking agents and albuterol inhibit the effect of each other.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Albuterol sulfate, like other agents in its class, caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a 2-year study in the rat, at oral doses corresponding to 10, 50, and 250 times the maximum human nebulizer dose. In another study, this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice and a lifetime study in hamsters revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.

**Pregnancy** - *Teratogenic Effects* - **Pregnancy Category C:** Albuterol has been shown to be teratogenic in mice when given subcutaneously in doses corresponding to the human nebulization dose. There are no adequate and well-controlled studies in pregnant women. Albuterol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. A reproduction study in CD-1 mice with albuterol (0.025, 0.25, and 2.5 mg/kg subcutaneously, corresponding to 0.1, 1 and 12.5 times the maximum human nebulization dose, respectively) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg. None were observed at 0.025 mg/kg. Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at 50 mg/kg, corresponding to 250 times the maximum human nebulization dose.

**Labor and Delivery:** Oral albuterol has been shown to delay preterm labor in some reports. There are presently no well-controlled studies which demonstrate that it will stop preterm labor or prevent labor at term. Therefore, cautious use of Albuterol Sulfate Inhalation Solution is required in pregnant patients when given for relief of bronchospasm so as to avoid interference with uterine contractibility.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in some animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** Safety and effectiveness of albuterol inhalation solution and solution for inhalation in pediatric patients below the age of 12 years have not been established.

**ADVERSE REACTIONS**

The results of clinical trials with Albuterol Sulfate Inhalation Solution in 135 patients showed the following side effects which were considered probably or possibly drug related:

*Central Nervous System:* tremors (20%), dizziness (7%), nervousness (4%), headache (3%), insomnia (1%).

*Gastrointestinal:* nausea (4%), dyspepsia (1%).

*Ear, Nose and Throat:* pharyngitis (<1%), nasal congestion (1%).

*Cardiovascular:* tachycardia (1%), hypertension (1%).

*Respiratory:* bronchospasm (8%), cough (4%), bronchitis (4%), wheezing (1%).

No clinically relevant laboratory abnormalities related to Albuterol Sulfate Inhalation Solution administration were determined in these studies.

In comparing the adverse reactions reported for patients treated with Albuterol Sulfate Inhalation Solution with those of patients treated with isoproterenol during clinical trials of 3 months, the following moderate to severe reactions, as judged by the investigators, were reported. This table does not include mild reactions.

Percent Incidence of Moderate to Severe Adverse Reactions

| Reaction | Albuterol N=65 | Isoproterenol N=65 |
|---|---|---|
| **Central Nervous System** | | |
| Tremors | 10.7% | 13.8% |
| Headache | 3.1% | 1.5% |
| Insomnia | 3.1% | 1.5% |
| **Cardiovascular** | | |
| Hypertension | 3.1% | 3.1% |
| Arrhythmias | 0% | 3.0% |
| *Palpitation | 0% | 22.0% |
| **Respiratory** | | |
| **Bronchospasm | 15.4% | 18.0% |
| Cough | 3.1% | 5.0% |
| Bronchitis | 1.5% | 5.0% |
| Wheeze | 1.5% | 1.5% |
| Sputum Increase | 1.5% | 1.5% |
| Dyspnea | 1.5% | 1.5% |
| **Gastrointestinal** | | |
| Nausea | 3.1% | 0 |
| Dyspepsia | 1.5% | 0 |
| **Systemic** | | |
| Malaise | 1.5% | 0 |

*The finding of no arrhythmias and no palpitations after albuterol administration in this clinical study should not be interpreted as indicating that these adverse effects cannot occur after the administration of inhaled albuterol.

**In most cases of bronchospasm, this term was generally used to describe exacerbations in the underlying pulmonary disease.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of inhaled albuterol.

**OVERDOSAGE**

Manifestations of overdosage may include anginal pain, hypertension, hypokalemia, and exaggeration of the pharmacological effects listed in **ADVERSE REACTIONS**.

The oral $LD_{50}$ in rats and mice was greater than 2,000 mg/kg. The inhalational $LD_{50}$ could not be determined.

There is insufficient evidence to determine if dialysis is beneficial for overdosage of Albuterol Sulfate Inhalation Solution.

**DOSAGE AND ADMINISTRATION**

The usual dosage for adults and children 12 years and older is 2.5 mg of albuterol administered 3 or 4 times daily by nebulization. More frequent administration or higher doses are not recommended. To administer 2.5 mg of albuterol, dilute 0.5 mL of the 0.5% inhalation solution to a total volume of 3 mL with sterile normal saline solution and administer by nebulization. The flow rate is regulated to suit the particular nebulizer so that the Albuterol Sulfate Inhalation Solution will be delivered over approximately 5 to 15 minutes.

The use of Albuterol Sulfate Inhalation Solution can be continued as medically indicated to control recurring bouts of bronchospasm. During treatment, most patients gain optimum benefit from regular use of the nebulizer solution.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately, as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

**HOW SUPPLIED**

Albuterol Sulfate Inhalation Solution 0.5% is a clear, colorless to light yellow sterile solution, and is supplied in amber glass bottles of 20 mL fill (NDC 50383-741-20) with accompanying calibrated dropper; boxes of one. **Store between 2° and 25°C (36° and 77°F).**

**Manufactured by**
**HI-TECH PHARMACAL CO., INC.**
**Amityville, NY 11701**

Rev. 10/97
MG #11208

---

Note: Use only as directed by your physician. More frequent administration or higher doses are not recommended.

**Store Albuterol Sulfate Inhalation Solution, 0.5%* between 2° and 25°C (36° and 77°F).**

ADDITIONAL INSTRUCTIONS:

| | | |
|---|---|---|
| **Systemic** | | |
| Malaise | 1.5% | 0 |

*The finding of no arrhythmias and no palpitations after albuterol administration in this clinical study should not be interpreted as indicating that these adverse effects cannot occur after the administration of inhaled albuterol.

**In most cases of bronchospasm, this term was generally used to describe exacerbations in the underlying pulmonary disease.

Rare cases of urticaria, angioedema, rash, bronchospasm, and oropharyngeal edema have been reported after the use of inhaled albuterol.

**OVERDOSAGE**

Manifestations of overdosage may include anginal pain, hypertension, hypokalemia, and exaggeration of the pharmacological effects listed in **ADVERSE REACTIONS**.

The oral $LD_{50}$ in rats and mice was greater than 2,000 mg/kg. The inhalational $LD_{50}$ could not be determined.

There is insufficient evidence to determine if dialysis is beneficial for overdosage of Albuterol Sulfate Inhalation Solution.

**DOSAGE AND ADMINISTRATION**

The usual dosage for adults and children 12 years and older is 2.5 mg of albuterol administered 3 or 4 times daily by nebulization. More frequent administration or higher doses are not recommended. To administer 2.5 mg of albuterol, dilute 0.5 mL of the 0.5% inhalation solution to a total volume of 3 mL with sterile normal saline solution and administer by nebulization. The flow rate is regulated to suit the particular nebulizer so that the Albuterol Sulfate Inhalation Solution will be delivered over approximately 5 to 15 minutes.

The use of Albuterol Sulfate Inhalation Solution can be continued as medically indicated to control recurring bouts of bronchospasm. During treatment, most patients gain optimum benefit from regular use of the nebulizer solution.

If a previously effective dosage regimen fails to provide the usual relief, medical advice should be sought immediately, as this is often a sign of seriously worsening asthma which would require reassessment of therapy.

**HOW SUPPLIED**

Albuterol Sulfate Inhalation Solution 0.5% is a clear, colorless to light yellow sterile solution, and is supplied in amber glass bottles of 20 mL fill (NDC 50383-741-20) with accompanying calibrated dropper; boxes of one. **Store between 2° and 25°C (36° and 77°F).**

**Manufactured by**
**HI-TECH PHARMACAL CO., INC.**
**Amityville, NY 11701**

Rev. 10/97
MG #11208

---

Note: Use only as directed by your physician. More frequent administration or higher doses are not recommended.

**Store Albuterol Sulfate Inhalation Solution, 0.5%* between 2° and 25°C (36° and 77°F).**

ADDITIONAL INSTRUCTIONS:

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 074543

## CHEMISTRY REVIEW(S)

Chem Closed

1. **REVIEW NUMBER**: 6

2. **ANDA**: 74-543

3. **NAME AND ADDRESS OF APPLICANT**:
Hi-Tech Pharmacal Co., Inc.
369 Bayview Avenue
Amityville, NY 11701

4. **LEGAL BASIS FOR ANDA SUBMISSION**: See CR #1.

5. **SUPPLEMENT(S)**: N/A

6. **DRUG NAME**: Albuterol Sulfate Solution for Inhalation, 0.5%

7. **NONPROPRIETARY NAME**: N/A

8. **SUPPLEMENT(S) PROVIDE(S) FOR**: N/A

9. **AMENDMENTS AND OTHER DATES**:
Firm:
Original submission: 9-19-94
11-10-94: Response to refuse to file letter dated 11-10-94
Amendment: 7-26-95 (Response to NA letter dated 5-25-97)
NC: 11-30-95 (Request for meeting)
Amendment: 1-22-96 (Response to NA letter dated 12-15-95)
Meeting Request: 6-14-96
Container sample: 6-17-96 (to Dr. Liu's attention).
Amendment: 11-4-96 (Response to NA letter dated 5-15-96)
Amendment: 1-17-97 (Sterile assurance amendment)
Major Amendment: 5-19-97
NC: 6-3-97
NC: 6-10-97(2)
NC: 8-8-97
* Fax Amendment: 11-5-97 (Response to 10-29-97 NA letter)

FDA:
Receipt of the ANDA submission: 9-20-94
Refuse to file letter: 11-10-94
Acknowledgment of ANDA submission: 12-19-94
NA (MAJOR): 5-25-95 (from CR #1 by Shing Liu)
NA (MAJOR): 12-15-9 (from CR #2 by Shing Liu)
NA (MAJOR): 5-15-96 (from CR #3 by Shing Liu)
NA (Major): 5-9-97 (From CR # 4 by Shing Liu)
NA (Fax): 10-29-97 (From CR # 5 by M. Shaikh)

10. **PHARMACOLOGIC CATEGORY**: Bronchodilator

11. **HOW DISPENSED**: Rx

12. **RELATED INDs, NDAs and DMFs**:

(b)4 - Confidential Business

(b)4 - Confidential Business

13. **DOSAGE FORM:** Solution

14. **POTENCY:** 0.5%

15. **CHEMICAL STRUCTURE AND NAME:** See USP 23

16. **RECORDS AND REPORTS:** N/A

17. **COMMENTS:**
1. Microbiological deficiencies has been identified per micro review dated 11-21-97 completed by A. High. These deficiencies are being communicated to the firm via telephone by A. High.

2. FPL became acceptable after review of amendment dated 11-5-97 completed by C. Holquist on 11-13-97 .

3. EER is acceptable as of report generated on 10-23-97.

18. **CONCLUSIONS/RECOMMENDATIONS:**
Approved pending satisfactory response for microbiological deficiencies identified in micro review dated 11-21-97.

19. **REVIEWER:**
Mujahid L. Shaikh

**DATE COMPLETED:**
11-28-97
Revised 12-2-97

cc: ANDA 74-543
ANDA DUP
Division File
Field Copy

Endorsements:

/S/ 12/2/97

HFD-625/MShaikh/12-2-97
HFD-625/MSmela, PM/12-2-97
x:\new\firmsam\hitech\ltrs\rev\74543rev.6
F/t by: bc/12-2-97

/S/ 12/4/97

Amendments of 12/4 and 12/18/97 found acceptable for stability by Dr. High in review dated 12/19/97

/S/ 12/25/97

# OFFICE OF GENERIC DRUGS, HFD-620
## Microbiologist's Review #6
## December 18, 1997

A. 1. **ANDA** 74-543

APPLICANT Hi Tech
369 Bayview Avenue
Amityville New York 11701

2. PRODUCT NAMES: Albuterol Sulfate Inhalation Solution

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 0.5%, Aqueous sterile oral inhalation solution, 20 mL fill in a 22 mL Multiple-dose bottle with calibrated dropper

4. METHOD(S) OF STERILIZATION: **Aseptic Fill**

5. PHARMACOLOGICAL CATEGORY: Bronchodiltor

B. 1. DATE OF INITIAL SUBMISSION: September 19, 1994

2. DATE OF TELEPHONE AMENDMENT: December ~~9~~ 18, 1997 **Subject of this Review**

3. RELATED DOCUMENTS: None

4. ASSIGNED FOR REVIEW: 12/18/97

C. REMARKS: The applicant has responded to the Microbiology Deficiency presented in the Telephone ~~Amendment~~ Conversation dated December 9, 1997.

D. CONCLUSIONS: The submission is recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. REVIEW NOTES".

/S/ 12/19/97
Andrea S. High, Ph. D.

cc: Original **ANDA**
Duplicate **ANDA**
Division Copy
Field Copy
Drafted by A. High, HFD 620 x:wp\microrev\74-543a5
Initialed by R. Patel

Patel 12/19/97

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER 074543

## BIOEQUIVALENCE REVIEW(S)

MAY 15 1995

Albuterol Sulfate Solution
for Inhalation, 0.5%
ANDA #74-543
Reviewer: Moo Park
Filename:74543W.994

HI-TECH Pharmacal
Amityville, New York
Submission Date:
September 19, 1994

Review of a Waiver Request

I. Objective

Review of a HI-TECH's waiver request on its Albuterol Sulfate Solution for Inhalation, 0.5%. The reference product is Schering's Proventil$^{R}$, 0.5%.

II. Formulation Comparison

The test and reference products contain the same active and inactive ingredients in the same quantity except sodium chloride. Sodium chloride is not inicated in PDR but shown in the Drug Product Reference File for the reference product. Since the product is supposed to be diluted with sterile normal saline before use, it will not affect the performance of the drug product whether sodium chloride is present or not. The formulation of the test product is shown in Table 1.

Table 1. HI-TECH's Formulation

| Ingredients | Quantity, W/V % |
|---|---|
| Albuterol Sulfate, USP | 0.5 |
| Benzalkonium Chloride, NF | 0.01 |
| Purified Water, USP | qs |
| Sulfuric Acid | qs to pH 3-5 |

III. Comments

1. The dosage form of the test and reference product is solution for inhalation. The active and inactive ingredients of the test and reference products are equivalent to each other qualitatively and quantitatively except sodium chloride.

2. The waiver request is granted for the test product.

IV. Recommendation

The Division of Bioequivalence agrees that the information submitted by HI-TECH demonstrate that Albuterol Sulfate Solution for Inhalation, 0.5%, falls under 21 CFR Section 320.22 (b) of the Bioavailability/ Bioequivalence Regulations. The waiver of

in vivo bioequivalence study for HI-TECH's Albuterol Sulfate Solution for Inhalation, 0.5%, is granted. HI-TECH's Albuterol Sulfate Solution for Inhalation, 0.5%, is deemed bioequivalent to Schering's Proventil$^{R}$, 0.5%.

The firm should be informed of the recommendation.

/S/

Moo Park, Ph.D.
Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE

/S/ 5/15/95

Ramakant M. Mhatre, Ph.D.
Branch Chief, Review Branch III
Division of Bioequivalence

Concur: /S/ Date: 5/15/95

Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74-543 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-658 (Mhatre, Park), Drug File, Division File